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The contribution of peripheral nerves to the pleasure from scratching an itch: Evidence from a neuronopathy participant

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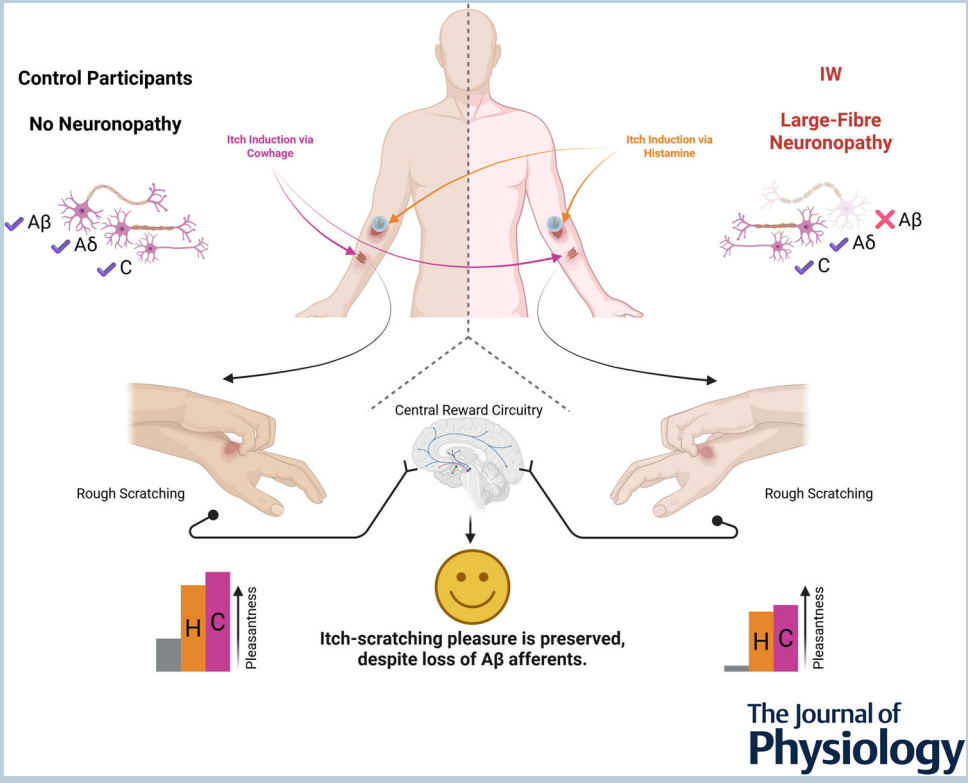

Abstract figure legend Acute itch was experimentally induced using histamine and cowage in control participants (with no neuronopathy) and in IW, a participant with a large-fibre sensory neuronopathy resulting in the loss of Aβ afferent function below C3, at the same time as largely preserving Aδ and C-fibre function. Peripheral sensory input is known to interact with central reward circuitry to mediate itch relief and the hedonic aspects of scratching. During a multistimulus psychophysics protocol following itch induction, rough scratching was rated as pleasant by both controls and IW. The preservation of scratching-induced pleasure in the absence of Aβ afferent input indicates a substantial contribution of Aδ and/or C-fibre afferents to the peripheral signalling associated with scratching reward in itch.

Abstract Itch is 'an unpleasant sensation of the skin commonly triggering an urge to scratch'. In chronic itch, the persistent itch/scratch cycle is reinforced and sustained by the intense pleasure

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and reward gained from scratching – sometimes after the itch has been abolished, and despite negative consequences. Scratching an itch recruits multiple areas of the limbic system that control addictive behaviours such as craving and intense pleasure seeking. It is hypothesised here that the pleasure derived from scratching is significantly influenced by small-fibre afferent input, including Aδ and C-tactile afferents. Subjective and physiological responses to acute itch and scratching were obtained from control participants, and compared with responses from IW, a participant with a well characterised large-fibre sensory neuronopathy below C3. In the forearm, IW's responses to temperature change, and physiological responses to histamine iontophoresis (wheal and axon reflex flare) match control participants. IW perceived both histamine- and cowage-induced itch, although self-reported peak intensities were lower than for controls and required a greater dose to elicit a comparable itch percept. Rough, scratching touch was rated significantly more intensely on itchy skin by both control participants and IW, and improved touch localisation in IW. Scratching an itch on the forearm is pleasurable for IW, despite the lack of large, myelinated fibres, thereby supporting the hypothesis that mechanosensitive small-fibre afferents contribute to the pleasure of scratching an itch.

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Key points

- Both histamine- and cowage-induced itch perception are preserved in a patient with large fibre neuronopathy.
- Gentle, dynamic touch (optimally activating C-tactile afferents) is significantly less pleasant on itchy skin, in control participants.
- As expected, scratching itchy skin is pleasant in control participants.
- The pleasure of scratching persists in a patient lacking large myelinated (Aβ) fibres, suggesting that small-fibre afferents, that is, Aδ and/or C-fibres such as C-tactile afferents, mediate some of this sensation.
- These findings provide insight into the peripheral neural mechanisms underlying itch relief, and may inform approaches to chronic itch management.

Introduction

'*Scratching an itch with a violence that would cause pain elsewhere may be experienced as one of the most exquisite of pleasures*' (Bishop, 1948)

Pruritus, or itch, was first defined by German physician Samuel Hafenreffer over 350 years ago as 'an unpleasant sensation of the skin leading to the desire to scratch' (Savin, 1998). A variation of this definition is still recognised today (Ständer et al., 2026). As with pain,

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it is also an unpleasant symptom of several different pathologies, both peripheral and central (Binder et al., 2008; Butler et al., 2024; Ikoma et al., 2006; Lavery et al., 2016). Acute itch is a common experience that triggers an intense urge to scratch the site of the itch, which is readily located, and to therefore suppress it. Compulsive, reward seeking behaviour, is more often observed if the site is not readily accessible; for example, on the middle of the back or with phantom itch (Bernhard, 1992). Chronic itch, with a lifetime incidence of up to 25.5% (Bollemeijer et al., 2025; Mollanazar et al., 2015; Roh et al., 2022), is recognised as being as distressing as chronic pain and is often associated with a significant negative impact on quality of life, as well co-occurring mental health conditions, including depression and anxiety (Carr et al., 2014; Kini et al., 2011). In addition, in chronic itch, rather than providing relief, the uncontrollable compulsion to scratch can exacerbate the underlying problem, leading to skin irritation, prolonged wound healing, potential infections and sleep disturbances (Ikoma et al., 2006; Yosipovitch et al., 2003). Although clinically relevant, the mechanisms underpinning the urge to scratch an itch have been under-studied (Li et al., 2024), and, in particular, the cutaneous nerve fibres that drive reward and *pleasure* from scratching an itch, the probable source of the compulsive motivation, are unclear.

The skin is innervated by myelinated Aβ and Aδ nerve fibres, and unmyelinated C-fibres. Biopsies from hairy skin sites reveal a dense innervation of unmyelinated sensory nerves, alongside the innervation of hair follicles and Merkel complexes by myelinated nerves. There are also populations of sympathetic autonomic nerves innervating sweat glands and blood vessels. Glabrous skin has a different pattern of innervation, with a larger population of myelinated to unmyelinated nerve fibres (Provitera et al., 2007). The major class of peripheral nerves associated with driving an affective state are the C-fibres (but see Nagi et al., 2019), as is clearly seen with activation of thermoreceptors, nociceptors, pruriceptors and 'hedonoceptors', comprising C-low threshold mechanoreceptors (CLTM), which were more recently discovered (in humans), and commonly known as C-tactile afferents (CT) (McGlone et al., 2014). Because C-fibres typically encode for sensations associated with a positive or negative valence (McGlone & Reilly, 2010), it is hypothesised that some of the pleasure derived from scratching an itch is also mediated (or contributed to) by C-fibres (Hashimoto & Yosipovitch, 2019).

The singular sensation of itch can have multiple causative mechanisms, molecular, neural and even social (Mahmoud et al., 2023; Ständer et al., 2007). Histamine, an endogenous inflammatory mediator was once considered to be the 'final common arbiter' of itch, but recent evidence has highlighted histamine-independent itch pathways, signalled by, for example, cowage (*Mucuna pruriens*) (Reddy et al., 2008) and chloroquine (Tang et al., 2024). Studies into the neurobiological mechanisms of itch transduction (Bautista et al., 2014; Dong & Dong, 2018; Ikoma et al., 2006; Prajapati et al., 2024) show that itch is a mostly C-fibre mediated sensation, dependent on the peripheral activation of a class of C-nociceptors that are sensitive to pruritogens, or on itch-specific C-pruriceptors. Pruritogens depolarise subpopulations of cutaneous primary C-fibre afferents, relaying via spinal neurons that project through the spinothalamic tract, and activating numerous cortical sites (Andrew & Craig, 2001; Marshall & McGlone, 2020; Mochizuki et al., 2014; White & Sweet, 1969). Neuroimaging studies have identified itch activations in primary and secondary somatosensory cortex, insular cortex (IC), anterior cingulate (ACC) and orbitofrontal cortex (OFC), reflecting the dual nature of itch being both sensory/evaluative *and* affective / motivational, as is the case for pain (Mochizuki et al., 2014, 2017; Setsu et al., 2021).

It has long been recognised that itch shares many common features with pain (McMahon & Koltzenburg, 1992; Davidson & Giesler, 2010; Forster & Handwerker, 2014) in that it provokes an attention-capturing motivation to alleviate the cause. With itch this is often achieved by scratching, which recruits multiple areas of the limbic system that also control addictive behaviours such as craving and intense pleasure seeking – leading to both relief and pleasure (Mochizuki et al., 2014, 2017; Papoiu et al., 2013; Setsu et al., 2021; Su et al., 2019; Vierow et al., 2009). It has been observed that scratching non-itchy skin is unpleasant or even painful, whereas scratching itchy skin is rated as highly pleasant (Ayres, 1964; Ikoma et al., 2006; Bin Saif, Papoiu et al., 2012), which begs the question 'what are the peripheral mechanisms?' that is, which primary afferents contribute to this context-dependent change in hedonic evaluation, from painful to pleasurable? Because the scratching stimulus is potentially noxious, are relief and pleasure paradoxically also mediated by (Aδ/C) nociceptor input?

A first foray into this conundrum was reported by Mochizuki et al. (2017), employing a nerve compression block (mechanical pressure which temporarily impedes distal, large myelinated fibre function) to decouple the link between Aβ afferents, itch relief and pleasure. They found no difference in itch intensity between the blocked and non-blocked site, suggesting that itch is not primarily mediated by Aβ afferents. Scratching still relieved the itch, suggesting that alleviation was mediated by smaller, or unblocked afferents. However, scratching and rough brushing induced pleasantness was significantly lower (but not abolished) in the blocked hand, suggesting an Aβ afferent contribution to the reward, which, if we maintain the hypothesis of context-dependent nociceptor

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activation, may be, for example, ultra-fast mechanosensory nociceptors which respond preferentially to rough (*vs*. soft) stimuli (Nagi et al., 2019).

Here, we investigate itch and scratching perception in IW – a participant with a rare but well-characterised sensory neuronopathy that destroyed all large dorsal root ganglia, leading to a complete absence of large myelinated touch and proprioceptive nerves below C3 (Cole, 2016). Aδ and C-fibre function is not (significantly) affected, with IW responding to pain and itch stimuli, pleasant touch and temperature (Cole et al., 2006; Olausson et al., 2008). Alongside fast-conducting Aβ low-threshold mechanoreceptors, there are CTs that respond preferentially to low force dynamic touch (Löken et al., 2009). In highly controlled conditions, IW responds to CT stimulation (low force, stroking on hairy skin) reporting a faint sensation of pleasant touch. In a functional magnetic resonance imaging study with IW, CT directed touch showed activation of the dorsal posterior insular cortex, but not of somatosensory areas S1 and S2, indicating CTs are the afferent part of a touch system which processes the emotional, affiliative and rewarding properties of touch (Olausson et al., 2008).

In a step towards identifying the peripheral pathways involved, here, we aim to investigate whether mechanosensitive Aβ fibres are indeed *required* to experience the pleasure of scratching an itch. To address this question, a profile of the subjective and physiological responses to acute itch and scratching was first obtained from neurologically intact participants. These were then compared with responses from IW. It was expected that IW would perceive and respond to itch similarly to control participants. However, if IW also derived pleasure and reward from scratching an induced itch, despite the loss of large, myelinated fibres, we would have evidence consistent with an Aδ or C-fibre component of the itch-scratch reward mechanism. Here, we propose a conceptual model, in which itch, through peripheral and/or central mechanisms, alters the processing and hedonic evaluation of small-fibre mechanosensory input, contributing to the unusually rewarding nature of scratching an itch. This would be comparable to the context-dependent changes that occur in nociceptors after tissue damage; for example, *hyperalgesia*, comprising an exaggerated response to noxious stimuli, or *allodynia*, where previously innocuous touch is perceived as painful (Westlund, 2006).

Methods

Ethical approval

All participants provided their written, informed consent and the study protocol was approved by the Liverpool John Moores Research Ethics Committee (14/NSP/009). The study conformed to the standards set by the *Declaration of Helsinki*, except for registration in a database.

Participants

Twenty control participants (13 female, 7 male), aged 19–45 years (mean = 22.89 years, SD = 6.59 years) participated in the study, recruited either through a research participant database (and compensated for their time with shopping vouchers) or were first-year psychology undergraduates (participating for course credit). All participants completed a health questionnaire (including screening for allergies, skin conditions, diabetes, neurological issues and medications such as anti-histamines). The neuronopathy participant, IW, is male, aged 64 years at the time of testing, with no relevant skin conditions. IW's neuronopathy developed following a gastric infection 40 years prior to this study (Cole & Paillard, 1995; Cole, 2016). Psychophysical tests have verified that IW has not recovered any Aβ nerve fibre function in the affected areas (below neck level – C3) but largely retains normal somatosensory function and sensations; for example, touch, itch, pain and temperature above C3 (Liljencrantz et al., 2013; Olausson et al., 2008). Thus, it is also possible to compare itch in a neuronopathy-affected site (forearms) and an unaffected site (forehead).

Itch induction

Acute itch was chemically induced using histamine iontophoresis or separately with topical application of cowage. Histamine is known to excite H1 receptors on mechanically insensitive C-nociceptors (CMi His+), and also causes a characteristic axon reflex flare (Schmelz et al., 2003). Cowage-induced itch was used as a model of non-histaminergic itch, and was of clinical relevance for patients in whom anti-histamines offer little relief (Papoiu et al., 2011). The active ingredient is the pruritogen mucunain, which binds to proteinase-activated receptors PAR-2 and PAR-4, and has been shown to activate different populations of polymodal, mechanosensitive, C-nociceptors and Aδ fibres to cause an itch, but without an axon reflex flare (Papoiu et al., 2011; Ringkamp et al., 2011). An electronic response button and visual analogue scale (VAS) slider were used to monitor itch onset and intensity in real-time. If no itch/very low itch (<10/100) was reported after 3 min, the induction procedure was repeated (once), before moving on with the protocol.

Pilot trials with IW suggested a higher tolerance/higher dose requirements for the pruritogens to elicit a comparable itch percept, particularly on the forearm. Discussions with IW revealed that he has regularly experienced itch caused by nettle contact when

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working in a rural setting, which may explain a physiological/psychological tolerance. A comparable tolerance was observed in other participants with prior experience of intense itch (e.g. reaction to multiple mosquito bites). It has been inferred through sensory testing that small fibre sensory nerve fibre innervation and function is normal in IW.

Histamine itch and flowmetry. Iontophoresis of topically applied histamine was used to induce histamine-itch. For this, 1% w.v. histamine dihydrochloride and 2% w.v. methylcellulose (Sigma-Aldrich, Poole, UK) were mixed in distilled water and left for 24 h to form the hydrogel for iontophoresis. The histamine hydrogel was pipetted onto the skin at the positive terminal. The gel covered a circular area ∼8 mm in diameter. An adhesive foam ECG electrode was used as the cathode. The Iontophoresis controller (MIC1) and blood flow monitoring system (DRT4, connected via the AN02 analogue controller) were operated through Moorsoft DRT4 software, version 2.0 (Moor Instruments, Axminster, UK).

Forearm. Histamine-itch was induced twice: (1) Right forearm: using an iontophoresis chamber (MIC-ION1R-P1; Moor Instruments). Laser Doppler probes were secured at the centre, and adjacent to the chamber to allow for blood flow monitoring, as used to quantify the wheal and axon reflex flare (60 s baseline, + 5 min post iontophoresis). (2) Left forearm: using a manually held probe (Moor Instruments) immersed in the hydrogel. The itch was allowed to develop for 3 min. In Control participants, a constant current of 50 μA was applied for two 10 s periods, with a 5 s interval. For IW, a constant current of 200 μA was applied for three 20 s periods, with a 5 s interval. The higher value/longer duration for IW was determined during pilot trials.

Forehead. An iontophoresis chamber and blood flow monitoring was used as above. For Control participants, a constant current of 200 μA was applied for two 20 s periods, with a 5 s interval. The higher current and duration on the forehead was required to compensate for the difference in skin properties, and to induce a comparable itch sensation. Values were determined by pilot trials and dose-calculations based on existing literature (Bin Saif, Alajroush et al., 2012). For IW, a constant current of 200 μA was applied for three 20 s periods, with a 5 s interval.

Cowage itch. The spicules (fine hairs, isolated from the seed pod) were collected onto a cotton bud, and rubbed directly onto a 1 cm^2 skin site (left forearm/forehead) for 20 s. A strip of lightly-adhesive paper tape (Micropore; 3M, Maplewood, MN, USA) was used to remove any spicules from the skin immediately after application. The itch was allowed to develop for 3 min. For Control participants, pilot experiments determined that ∼20 spicules were required to induce a sufficiently strong itch in most control participants – consistent across both locations. For IW, ∼30 spicules were required to induce a comparable itch.

Skin sites

Forearm. Three 2 cm long sites were marked on the ventral forearm (7 cm apart), starting at the wrists. The first itch induction site was always the central site on the right forearm. Itch on the left forearm was induced at the distal and proximal sites; the pruritogen order was counterbalanced across participants. The distal and proximal sites on the right forearm, and the central site on the left forearm, where no itch was induced, acted as ipsilateral and contralateral control sites across all the trials.

Forehead. Two skin sites were marked on each side of the forehead, ∼4 cm apart (one itch and one ipsilateral control site on each side). Care was taken to avoid the midline (mixed innervation), and to ensure the areas to be tested fell within the typical trigeminal nerve boundary. The pruritogen order was counterbalanced across participants.

Psychophysical tests

Thermal thresholds. Thermal tests closely followed the relevant QST protocols (Rolke et al., 2006). Thermal stimuli were delivered by means of a computer-controlled thermode (30 × 30 mm, Pathway model ATS; Medoc, Ramat Yishai, Israel). Baseline temperature was set at 32°C, with 1°C s^{-1} rate of change. Participants responded, as instructed, with a button press. Following each response, the thermode returned to baseline; there was a ∼10 s interval before the next trial. Thermal thresholds were measured at the relevant ipsilateral and contralateral control sites before and after each itch induction. Detection thresholds: participants were asked to respond when they felt the thermode change in temperature – warming or cooling. Three consecutive repeats for each condition produced mean warm and cold detection thresholds. The order of warm *vs.* cool was counterbalanced across participants. Regarding pain thresholds, following both detection tests, participants were asked to respond when the thermode temperature change – hot or cold – became painful. Two consecutive repeats produced mean hot and cold pain thresholds. The order of hot *vs.* cold was counterbalanced across participants.

Brushing/scratching. There was a 3 min interval following the itch-induction procedure, after which

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experimenters delivered a manual brushing/scratching stimulus using soft and rough substrates (fleece blanket *vs*. scouring pad). Stimuli were delivered in pairs, to the itch site and a control site (the ipsilateral site or the corresponding contralateral site) with the same substrate, affixed to a force-controlled manual tactile stimulator (MTS) (0.22 N, six strokes per stimulus, at ∼3cm s^{-1}). Scratching stimuli were delivered to the participants rather than letting them scratch the itch to normalise force and velocity across participants. The order of the first stimulus pair (soft first or rough first) was counter-balanced across participants, and subsequently alternated. A numeric rating score was requested vocally after each stimulus, between –5 and +5 (very unpleasant to very pleasant, with 0 as neutral). At least six pairs of ratings were obtained per induced itch – six ratings per site (itch *vs*. control) and three ratings per substrate at each site.

Twelve Control participants (seven female, five male) and IW were also asked to compare the intensity of stimulus pairs (itch site *vs*. control site). Participants would be asked 'which was more intense?' and were asked to answer 'First' or 'Second' [two-answer forced choice (2AFC) paradigm].

Localisation. Pilot experiments showed that, unlike control participants, IW could not easily describe or locate a touch without visual, auditory or thermal cues as stimulus localisation relies largely on myelinated, discriminative, mechanoreceptors. Thus, in addition to the above, IW was asked to close his eyes during the brushing/scratching protocol, and verbally localise and describe each stimulus as well as possible (e.g. left *vs*. right/itchy site *vs*. non-itchy site/soft *vs*. rough). Care was taken to eliminate/minimise other cues.

Itch characterisation and intensity

Along with the electronic VAS, the Eppendorf Itch Questionnaire (0–4 scale, Darsow et al., 2001) was adapted (to remove irrelevant questions); the adapted EIQ (aEIQ) was presented to participants at the start of the session (to establish previous itch experience), and after itch each stimulus – used to characterise the itch and scratching, to understand how the participant might have dealt with it in normal circumstances, and to record peak itch intensity.

Statistical analysis

Analysis and statistical calculations were performed using Prism (GraphPad Software Inc., San Diego, CA, USA). Comparisons of thermal thresholds were between control participants and IW were corrected for multiple comparisons. Blood flowmetry analysis was conducted as a percentage of baseline (pre-itch induction). Brushing and scratching pleasantness were analysed using mixed–effects models [restricted maximum likelihood (REML)] to assess group–level differences in control participants, with Dunnett's post–hoc tests applied for pairwise comparisons between control and itch sites. Individual trials where the induced itch intensity was very low (<10/100) were considered a failure to induce an itch, and data from these trials were excluded from brushing/scratching analysis. Thye psychophysics data of one participant were removed entirely because of non-compliance. For IW, corrected unpaired Welch's *t* tests were used to compare ratings between control sites and itch sites. The primary focus of the statistical analysis is on within–group contrasts in control participants, and within–participant contrasts in IW, as a basis for evaluating the contribution of small, unmyelinated afferents to itch and scratching reward.

Results

Thermal thresholds

Pre-itch induction thermal thresholds measured typical Aδ and C-fibre function. By contrast to previous findings (Cole et al., 2006; Olausson et al., 2008), it was found that thermal thresholds for IW were largely consistent with control participants on both the forearm (Fig. 1) and the forehead, suggesting normal small fibre function across all sites. IW's cold pain threshold on the forearm is significantly different from the control participant mean ($P < 0.001$, SE = 2.549, d.f. = 190; Sidak's multiple comparison); however there was no significant difference between forearm and the normally-innervated forehead in IW, and the thresholds for both sites are within the normative range for QST, where there is a large variation in cold pain thresholds (Rolke et al., 2006).

Itch induction

Blood flowmetry measured the well-characterised wheal and axon reflex in real-time, showing the typical pattern of physiological responses to histamine iontophoresis. Response is measured as change in blood flow (arbitrary units) and calculated as a percentage of the mean baseline measurement for each individual. The 1° measurement is of the wheal at the iontophoresis site and the 2° measurement is of the axon reflex flare, from outside the chamber.

In the forearm of control participants, mean 1° blood flow post-iontophoresis was 541.8 ± 226% of baseline, and mean 2° blood flow post-iontophoresis was 197.3 ± 57.2% of baseline. In the forearm of IW, mean 1° blood flow post-iontophoresis was 287.1 ± 121.5% of baseline, and mean 2° blood flow post-iontophoresis was 132.5 ± 41.77% of baseline (Fig. 2).

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This supports previous reports that IW still has a response to pruritogens, and can perceive itch (Cole et al. 2006), and serves as further confirmation of intact peripheral C-fibre function in IW.

In the forehead of control participants, mean 1° blood flow post-iontophoresis was 461 ± 57.32% of baseline, and mean 2° blood flow post-iontophoresis was 128.1 ± 9.254% of baseline. In the forehead of IW, mean 1° blood flow post-iontophoresis was 211.6 ± 27.9% of baseline; a 2° axon reflex flare was not observed.

Itch quality (aEIQ)

Control participants. Descriptors with mean ratings ≥2 (out of 4) were considered elevated. For histamine, *itching* (2.54 ± 1.46), *urge to scratch* (2.43 ± 1.46) and *annoying* (2.20 ± 1.43) met this threshold. Cowhage produced a broader set, including *itching* (2.93 ± 1.33), *urge to scratch* (3.29 ± 1.14), *pricking* (2.57 ± 1.28), *stinging* (2.43 ± 1.45), *sharp* (2.29 ± 1.49), *painful* (2.21 ± 1.48) and prickling (2.21 ± 1.25). Worst memorable itch reports showed high endorsement of *painful*, *burning*, *stinging*, *sharp* and strong motivational descriptors.

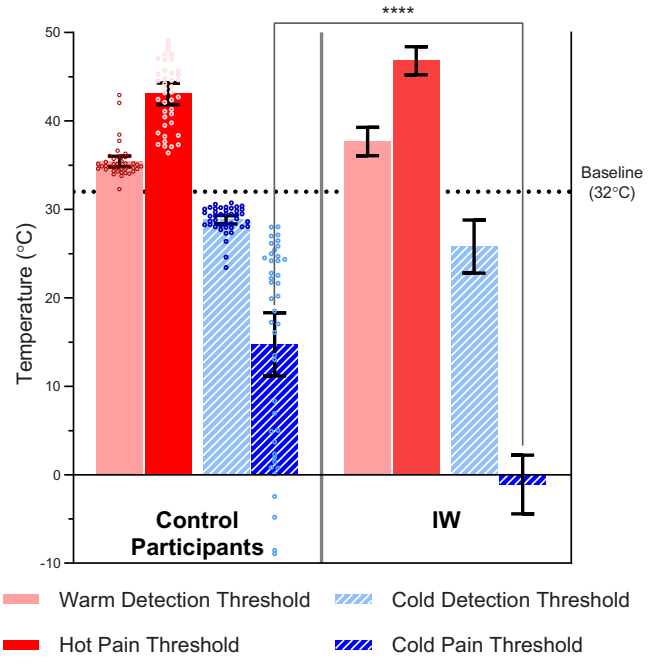

Figure 1. Pre-itch temperature threshold: forearm
Thermal change detection and thermal pain thresholds, on forearm control sites, pre-itch [mean + 95% confidence intervals (CIs)] and a comparison of thermal sensitivity between Control participants (right) and IW. (left). Baseline set at 32°C; QST standard for skin temperature. Detection threshold determined by first response to a change from baseline; pain threshold as temperature at which temperature increase or decrease first became painful. IW's cold pain threshold is significantly different from the mean for control participants, but within the expected variability for QST.

Descriptors for scratching the itch: for histamine, elevated descriptors were *satisfaction* (2.60 ± 1.23), *itch decreasing* (2.54 ± 1.01) and *physical urge* (2.46 ± 1.17). Cowhage produced higher and broader elevations, including *physical urge* (3.00 ± 0.84), *satisfaction* (2.71 ± 0.94), *permanent urge to scratch* (2.57 ± 1.14) and *itch decreasing* (2.50 ± 1.28). Worst memorable itch reports showed strong physical urge, compulsive qualities and high satisfaction from scratching. Descriptors for actions that *would* be taken against the itch: for histamine, only *scratching* (3.11 ± 1.59) and *scrubbing* (2.06 ± 0.73) exceeded the ≥2 threshold. Cowhage produced a similar pattern, with *scratching* (3.07 ± 1.65) and *scrubbing* (2.36 ± 1.44) most strongly endorsed. Worst memorable itch actions varied broadly, including *scratching*, *squeezing* and *pinching*.

IW. At the forearm, IW endorsed only low-level descriptors for histamine (all ≤1). For cowhage, only *piercing*, *tingling* and *prickling* reached moderate levels (all 2). At the forehead, histamine produced clearer endorsements, including *itching* at 3 and *tingling* and *prickling* at 2. For his worst memorable itch, located in a deafferented region, IW endorsed highly endorsed a broad variety of descriptors, including *burning*, *itching*, *urge to scratch*, *stinging* and others. Descriptors for scratching the itch: On the forearm, IW did not endorse any scratching-related descriptors above 1 for either pruritogen. On the scalp, *satisfaction* reached 2. For his worst memorable itch, he endorsed a strong scratching response, including *satisfaction* at 4 and *physical urge* at 3.

Descriptors for actions that *would* be taken against the itch: On the forearm, IW indicated *rubbing* and *scraping* at 1 for histamine and *rubbing* at 1 for cowhage. On the scalp, he reported *rubbing* at 4, and *applying ointment* at 2. For his worst memorable itch, he reported typical actions including *scratching*, *squeezing*, *pinching*, *digging fingernails*, *rubbing*, *cooling* and *applying ointment*.

Itch intensity (eVAS and aEIQ)

Forearm. There is a strong correlation at the group level between histamine induced itch intensity and mean blood flow. (Spearman – primary: $R = 0.856$, $P < 0.001$; secondary: $R = 0.797$, $P < 0.001$). Mean real-time itch intensity (electronic VAS, out of 100) during histamine trials was consistent for control participants (mean ± SD = 39 ± 19) and IW (mean ± SD = 30 ± 14); However, IW required a much greater dose of histamine in the forearm to induce a comparable itch intensity (maximum delivery ~13 µg for IW *vs.* ~1.2 µg for control participants). Self-reported peak intensity (post-hoc;

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questionnaire, 0 = No itch, 100 = worst imaginable itch) show more variance. Very low itch intensity trials (<10/100) were excluded from further analyses (histamine: 7%; cowage: 20%;).

In the forearm of control participants, the mean ± SD peak itch intensity for histamine itch was 60.8 ± 20.8, and the average peak itch intensity for cowage was 69.9 ± 20. For IW, the peak itch intensity for histamine was 38.8, and 31 for cowage. Given the evidence of relatively normal small fibre function in IW (Fig. 2), and the large individual differences in control participants, the difference between control participants and IW may be down to an acquired tolerance to itch, and individual differences in self-report, and use of the scale.

Forehead. There is a significant correlation at a group level, between itch intensity and mean blood flow (Spearman – primary: $R = 0.598$, $P < 0.001$; secondary: $R = 0.597$, $P < 0.001$). Self-reported peak intensity from the post-hoc questionnaire showed a wide range of responses. As above, trials with very low itch intensities (<10/100) were excluded from further analyses (histamine: 30%; cowage: 10%).

On the forehead of control participants, the average peak itch intensity for histamine was 52.3 ± 29.6), and for cowage was 60.2 ± 24.1). In IW, peak forehead intensities were 16.7 for histamine and 27.1 for cowage.

Soft brushing

Forearm. In control participants, the mixed–effects model (REML) revealed a significant main effect of treatment ($F_{1.859,29.74} = 10.79$, $P < 0.001$), indicating that pleasantness ratings differed across conditions. Dunnett's post–hoc comparisons confirmed that ratings were significantly lower on histamine sites compared to control (mean difference = 1.40, 95% confidence interval (CI) = 0.57–2.24, $P = 0.00150$) and on cowage

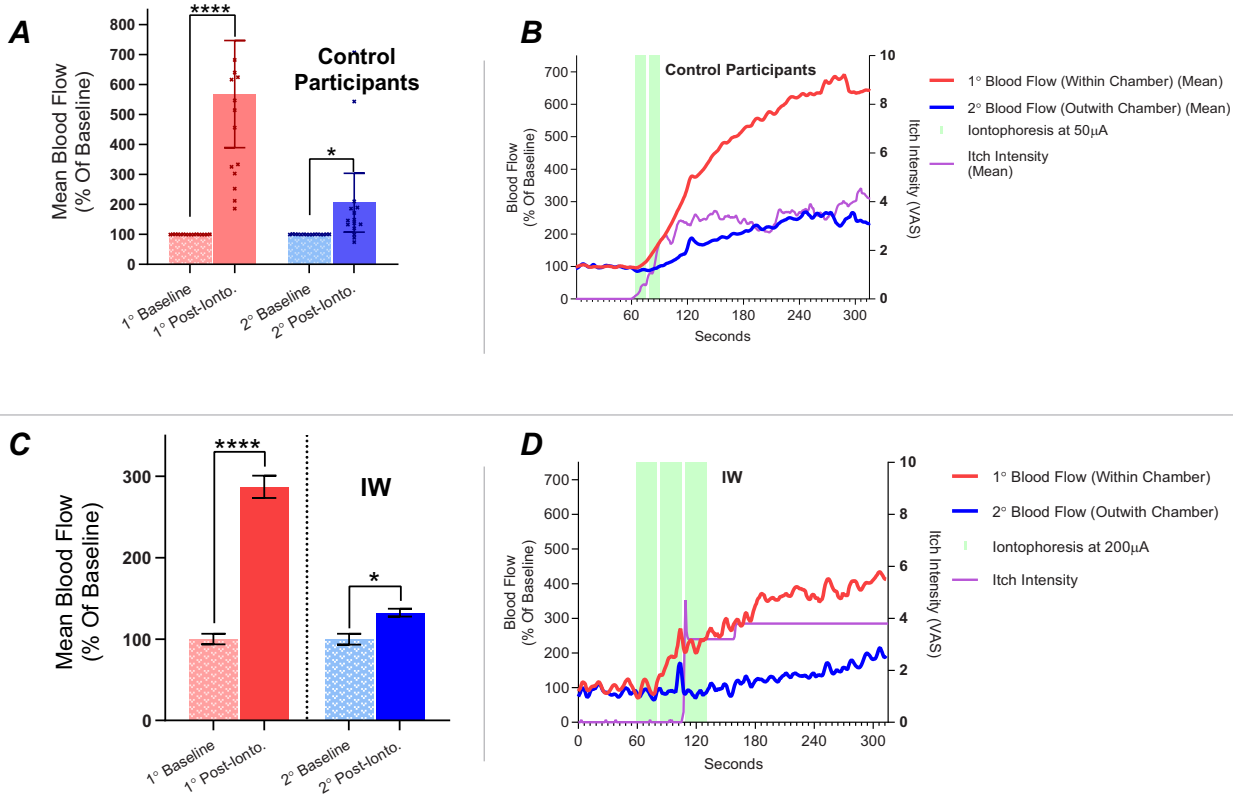

Figure 2. Laser Doppler measurement of blood flow during iontophoresis: forearm
Comparison of physiological responses to histamine-iontophoresis induced itch between Control participants and IW using laser Doppler blood flow measurement (Forearm). *A*, mean (±95% CI) blood flow as a percentage of baseline, before and after iontophoresis, in control participants, 1° = probe within the chamber, recording wheal (shown in red); 1° baseline *vs*. post: $P < 0.001$. 2° = probe adjacent to chamber, recording axon reflex flare (shown in blue); 2° baseline *vs*. post: $P = 0.0327$. Baseline (100%), determined per probe, as mean of 60 s prior to iontophoresis. Vertical bars represent periods of iontophoresis. *B*, real-time recording of blood flow (1° and 2°), itch intensity (electronic VAS) and iontophoresis periods, in control participants. *C*, mean (±95% CI) blood flow as a percentage of baselines, before and after iontophoresis: IW. 1° baseline *vs*. post: $P < 0.001$; 2° baseline *vs*. post: $P = 0.0128$. *D*, real-time recording of blood flow (1° and 2°), itch intensity and iontophoresis periods: IW.

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sites compared to control (mean difference = 0.91, 95% CI = 0.03–1.79, P = 0.0430) (Fig. 3*A*). Three participants reported that soft touch exacerbated the itch, suggesting induced alloknesis (increase in itch triggered by innocuous stimulation), akin to allodynia in pain (Simone et al., 1991). By contrast, IW generally rated soft brushing on the forearm as neutral (means close to zero across conditions), compatible with him not feeling the stimulus. Welch–corrected unpaired t tests revealed no significant difference between control and cowage sites ($t_{10.21}$ = 0.646, P = 0.533), whereas ratings on histamine sites were slightly higher than control ($t_{36.32}$ = 1.896, P = 0.0659), though this did not reach statistical significance. These results suggest a small, non–significant increase in forearm sensitivity following itch induction in IW.

Forehead. Control participants rated soft brushing as mildly pleasant across all conditions (control: mean ± SD = 1.66 ± 1.1, histamine: mean ± SD = 1.44 ± 1.2, cowage: mean ± SD = 1.06 ± 1.5), with no significant main effect of treatment. Dunnett's multiple comparisons confirmed no significant differences between control and histamine (mean difference = 0.23, 95% CI = –0.49 to 0.94, P = 0.639) or cowage (mean difference = 0.60, 95% CI = –0.30 to 1.50, P = 0.184) (Fig. 3*B*). On normally innervated skin, IW's pleasantness ratings to the same stimuli were comparable to those of control participants (control: mean ± SD = 2.08 ± 1.9, histamine: mean ± SD = 1.60 ± 0.5, cowage: mean ± SD = 1.67 ± 0.7). Welch–corrected unpaired t tests confirmed no significant differences between control and histamine ($t_{14.30}$ = 0.811, P = 0.430) or control and cowage ($t_{14.81}$ = 0.704, P = 0.492). IW was able to feel, identify and localise the stimuli on the forehead accurately.

The data suggest that the conscious perception of the pleasantness of the softer stimuli is reliant on Aβ afferents;

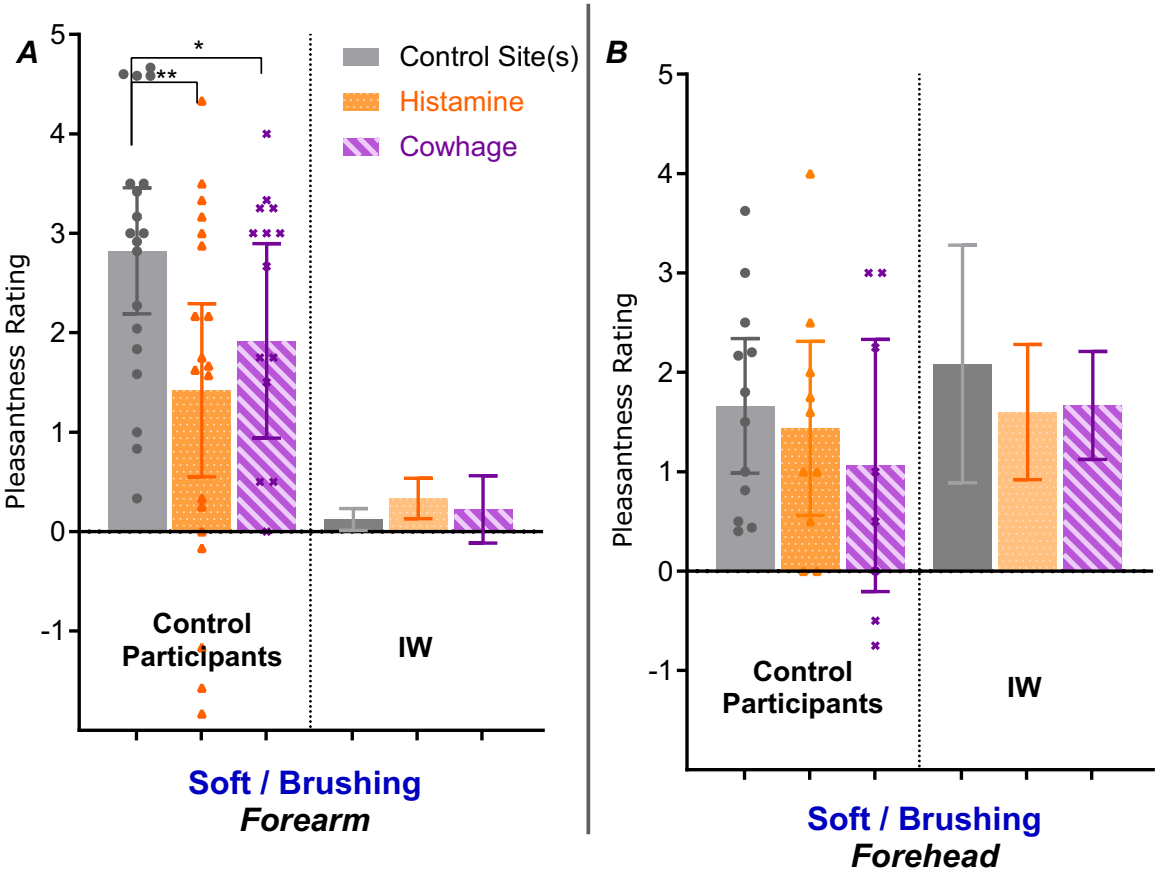

Figure 3. Pleasantness ratings – soft / brushing stimuli: forearm *vs.* forehead
A, comparison of mean pleasantness ratings (+95% CI) to soft/brushing stimuli applied to the forearm at control (no-itch), histamine and cowage skin sites in control participants, and IW. Control participants rate brushing itchy skin as significantly less pleasant. IW rated all brushing as neutral, or very mildly pleasant (no significance) because he could not adequately determine the touch. *B*, comparison of mean pleasantness ratings (+95% CI) to soft/brushing stimuli applied to the forehead. By contrast to the forearm, on average, all brushing was felt as pleasant on the forehead, regardless of site for control participants and IW. No significant differences were found.

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furthermore, soft dynamic touch to itchy skin appeared to be unfavourable, rather than rewarding, on the forearm but not on the forehead in controls.

Rough scratching

Forearm. In control participants, the mixed–effects model (REML) revealed a highly significant main effect of treatment ($F_{1.712, 27.39} = 33.09$, $P < 0.001$), indicating that pleasantness ratings after scratch differed across conditions. Dunnett's post–hoc comparisons confirmed that ratings were significantly higher on histamine sites compared to control (mean difference = –2.68, 95% CI = –3.71 to –1.66, $P < 0.001$) and on cowage sites compared to control (mean difference = –3.14, 95% CI = –4.39 to –1.89, $P < 0.001$) (Fig. 4*A*). IW rated the rough scratch stimuli as neutral on forearm control sites (mean ± SD = 0.27 ± 0.5, generally not felt). However, unlike with the brushing stimuli, IW rated scratching the itch sites as significantly more pleasant, although not as highly as control participants. Welch–corrected unpaired *t* tests confirmed that ratings were significantly higher on histamine sites compared to control ($t_{27.65} = 4.102$, $P < 0.001$) and on cowage sites compared to control ($t9.94 = 2.442$, $P = 0.0348$). Scratching an itch was therefore still pleasurable and rewarding for IW, despite the lack of large, myelinated fibres.

Forehead. The mixed-effects model indicated there was a non–significant main effect of treatment ($F_{0.2664, 2.131} = 9.681$, $\varepsilon = 0.1332$, $P = 0.0701$). However, control participants rated the rough scratching stimuli as neutral on forehead control sites (mean ± SD = 0.04 ±1.2), but as significantly more pleasant on itch sites (histamine: mean ± SD = 1.60 ±1.9, mean difference = –1.64, 95% CI = –2.99 to –0.29,

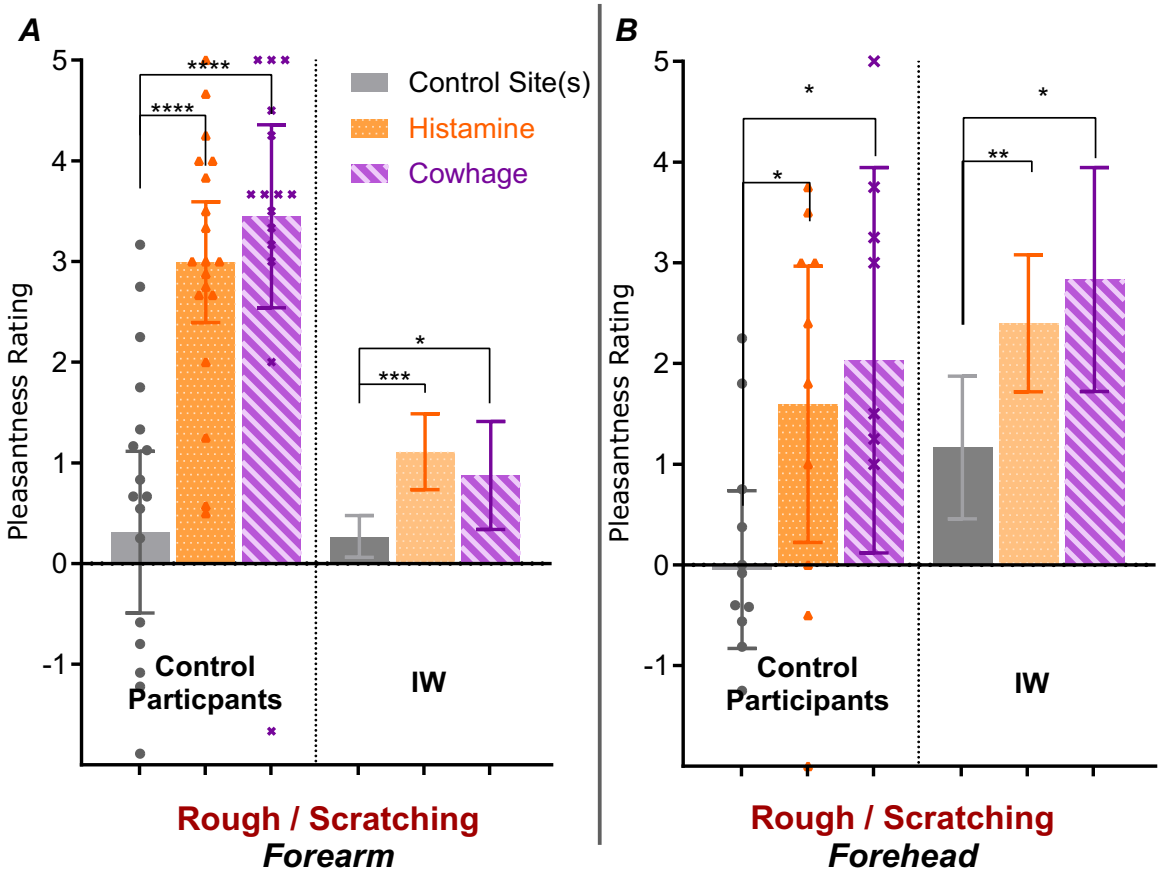

Figure 4. Pleasantness ratings – rough/scratching stimuli: forearm *vs*. forehead
A, comparison of mean pleasantness ratings (+95% CI) to rough/scratching stimuli applied to the forearm at control (no-itch), histamine and cowage skin sites. Scratching is significantly more pleasurable at itch sites, for both control participants and IW. *B*, comparison of mean pleasantness ratings (+95% CI) to rough/scratching stimuli applied to the forehead – the neurologically intact site in control participants and IW. IW rates scratching control sites on the forehead highly, but scratching the (cowage) itch site is still significantly more pleasurable. Overall there was no difference between controls and IW.

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$P = 0.0200$; cowage: mean ± SD = 2.03 ±2.3, mean difference = –2.08, 95% CI = –3.74 to –0.42, $P = 0.0191$; Dunnett's multiple comparisons). A similar response was seen with IW (Fig. 4*B*), who rated scratching on control sites as neutral (mean ± SD = 1.17 ± 1.1), but more pleasant on both histamine and cowage sites. Welch–corrected unpaired *t* tests confirmed that ratings were significantly higher on histamine sites compared to control ($t_{14.27} = 3.050$, $P = 0.00850$) and on cowage sites compared to control ($t_{18.67} = 2.783$, $P = 0.0120$). These findings indicate that IW experienced the scratching reward on the forehead in a manner consistent with control participants, an area in which he has a clinically normal large myelinated sensory afferent supply.

Pleasantness *vs.* itch intensity

The itch-induced change in pleasantness ratings correlate to itch intensity (histamine/scratching: $r = 0.5047$, $P = 0.0275$; cowage/scratching: $r = 0.6801$, $P = 0.00189$), suggesting the effect is dose-dependent (Fig. 5*A*). IW's pleasantness ratings (for scratching itch sites) are comparatively lower than the control participant mean; however, they fall within the 95% CIs.

Stimulus intensity (and localisation)

Soft stimuli. In the 2AFC paradigm, control participants did not show any bias between itch sites and control sites when comparing the intensity between two soft stimuli (% itch site chosen; Control participants: mean ± SD = 52.63 ± 7.4; IW: mean ± SD = 40 ± 25) (Fig. 6*A*). IW was also typically unable to describe or accurately localise the stimulus as there was no conscious percept (Fig. 6*B*).

Rough stimuli. Control participants considered the rough scratching stimuli significantly more intense on itchy skin than on control sites (% itch site chosen; mean ± SD = 81.94 ± 26.07%, $P = 0.00258$; difference from hypothetical mean of 50%) (Fig. 6*A*). IW similarly rated rough stimuli as more intense when delivered to itchy skin (mean ± SD = 86.87 ± 15.34%, $P < 0.001$) (Fig. 6*B*), even though he could only localise which

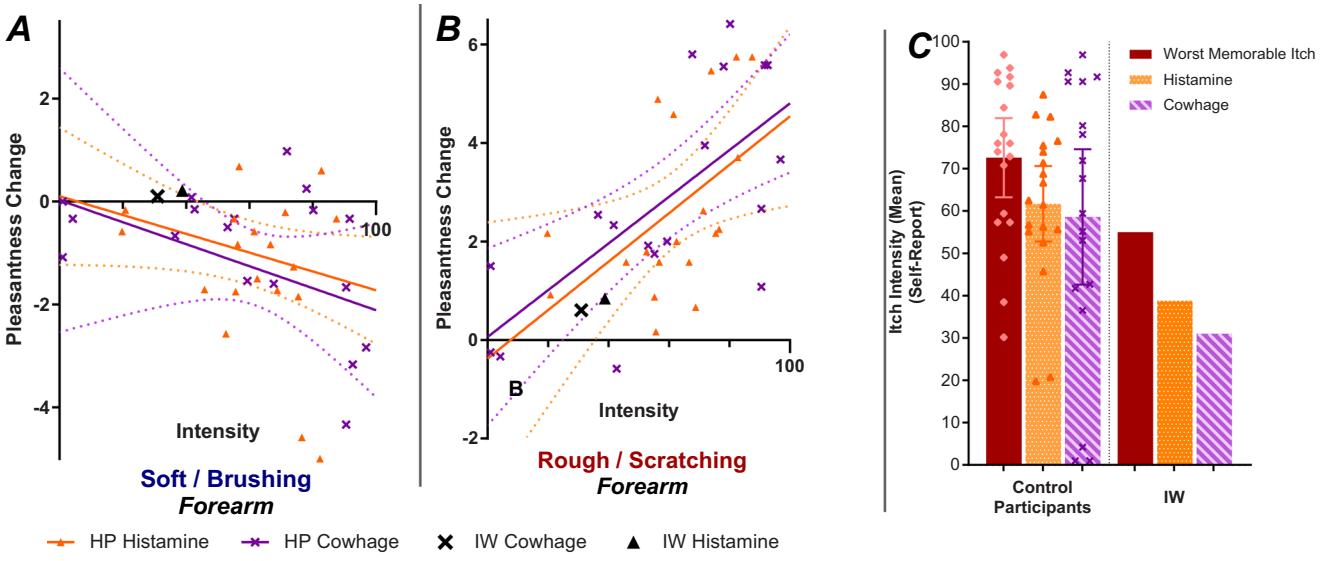

Figure 5. Itch intensity *vs.* pleasantness change: forearm
A, brushing: no significant correlation between itch intensity on forearm and brushing pleasantness; cowage (r = –0.4346, R^2 = 0.1889, P = 0.0715); histamine (r = –0.2642, R^2 = 0.06979, P = 0.274). Results from IW also fit within the 95% CIs, suggesting his responses were not atypical relative to controls. Solid lines denote trend lines – dotted lines denote 95% CIs. Symbols show the distribution of mean change in pleasantness rating (from control), per each itch condition, per participant, representing the individual differences in itch intensity. *B*, scratching: significant positive correlation between itch intensity on forearm and change in scratching-pleasantness ratings within control participants for both histamine ($r = 0.5047$, $R^2 = 0.2547$, $P = 0.0275$) and cowage ($r = 0.6801$, $R^2 = 0.4625$ $P = 0.00189$). Results from IW also fit within the 95% CIs, suggesting his responses were not atypical relative to controls. IW Cowage/Scratching: Intensity = 31; Pleasantness change = 0.6058. IW histamine/scratching: intensity = 38.8; pleasantness change = 0.8419. *C*, comparison of induced itch intensity on forearm, *vs.* 'worst memorable itch' (+95% CI; self-report) in control participants and in IW. Although there were individual differences in the self-reported intensity, particularly for individuals with prior experience of intense pruritic episodes, on average, we were able to induce an experimental itch analogous to participants' 'worst memorable itch', as recorded at the start of the experiment.

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site the stimulus was delivered to with 60% accuracy, suggesting that in IW, intensity, valence and location of the stimuli are being signalled independently, by different (unmyelinated) nerve fibres.

Discussion

Previous neuroimaging and behaviour studies have indicated that the pleasure and relief associated with scratching depends on central reward circuitry (Mochizuki et al., 2014; Papoiu et al., 2013; Setsu et al., 2021), which is modulated by peripheral afferent input, in neurologically intact participants (Mochizuki et al., 2017).

The findings of the present study show that scratching itchy skin is rated as pleasurable in both control participants and IW, despite his lack of Aβ fibres. By contrast, gentle brushing was less pleasant on itchy skin in controls, and neutral in IW (no conscious sensation, and presumably therefore, no valence). The slight (non-significant) variation in IW's post-itch pleasantness ratings to soft brushing could indicate some change in sensitivity.

Ratings for pleasantness to a scratching stimulus in the control group were significantly higher in itchy compared to non-itchy skin, with a clear correlation to itch intensity as seen previously (Bin Saif, Papoiu et al., 2012) – the stronger the itch, the more rewarding the scratch. Indeed, pleasantness ratings to scratching itchy skin were as high as those delivered using soft, gentle brushing to non-itchy skin, a stimulus associated with preferential CT activation and positive emotional aspects of touch (McGlone et al., 2014). Scratching the skin activates all types of mechanosensitive afferents (Fig. 7) and, although such a stimulus would disproportionally activate high threshold mechanosensitive afferents of all types (C, Aδ and Aβ-nociceptors), there will also be substantial input to the dorsal horn from CTs, and from low threshold Aβ fibres (in those without large-fibre neuronopathy).

The aEIQ data shows that self-reported experience of (worst memorable) itch in IW is consistent with control participants, with strong nociceptive and motivational descriptors and typical scratching behaviours even in the absence of Aβ input. For acute, experimentally induced itch IW required larger pruritogen doses and reported lower peak intensities than controls, and his aEIQ induced–itch descriptor endorsements at the forearm were relatively sparse suggesting some attenuation in perception, or reduced qualitative richness. However, there was a clear physiological and behavioural response to itch induction. High pleasantness ratings for scratching histamine or cowage induced itch were retained in IW,

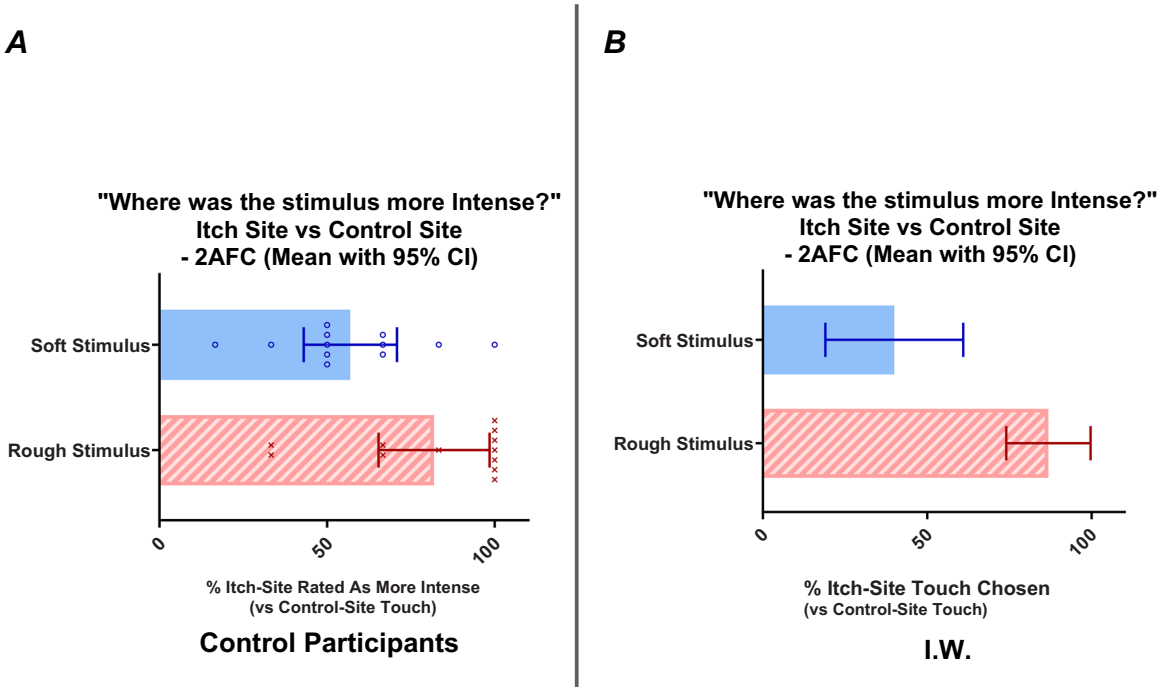

Figure 6. 2AFC: comparison of stimulus intensity across itch *vs*. control site
Percentages represent times the same stimulus was considered more intense when delivered to itchy skin. *A*, control participants (n = 12) – Soft: mean ± SD = 56.94 ±21.86 (P = 0.463) (Data points represent mean percentage of times each participant selected the itch site). Rough: mean ± SD = 81.94 ± 26.07% (P = 0.00258; difference from hypothetical mean of 50%). *B*, IW – Soft: IW: mean ± SD = 40 ± 25 (P = 0.461). Rough: mean ± SD = 86.94 ± 15.34% (P < 0.001; difference from hypothetical mean of 50%).

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in contrast to previous studies using nerve compression block (Mochizuki et al., 2017). This suggests that (at least some) positive hedonic valence to scratching an itch is preserved despite the absence of Aβ mechanosensitive afferent activity.

Although it is clear that a single-case study limits the conclusions we can draw, the selective-dissociation observed in IW is informative, and the differences observed between IW and controls provide a foundation for refining the hypotheses about fibre-specific, or labelled-line, mechanisms involved in the hedonic aspects of itch relief.

Because IW has maintained function in C-fibre modalities (Liljencrantz et al., 2013; Olausson et al., 2008) (Fig. 1), probably including CT afferents (Olausson et al., 2002), and given that activity in CT afferents is already associated with pleasant emotional aspects of touch, could activation of these fibres be the primary peripheral mediator for the pleasure of scratching an itch? Intuitively, this may seem improbable.

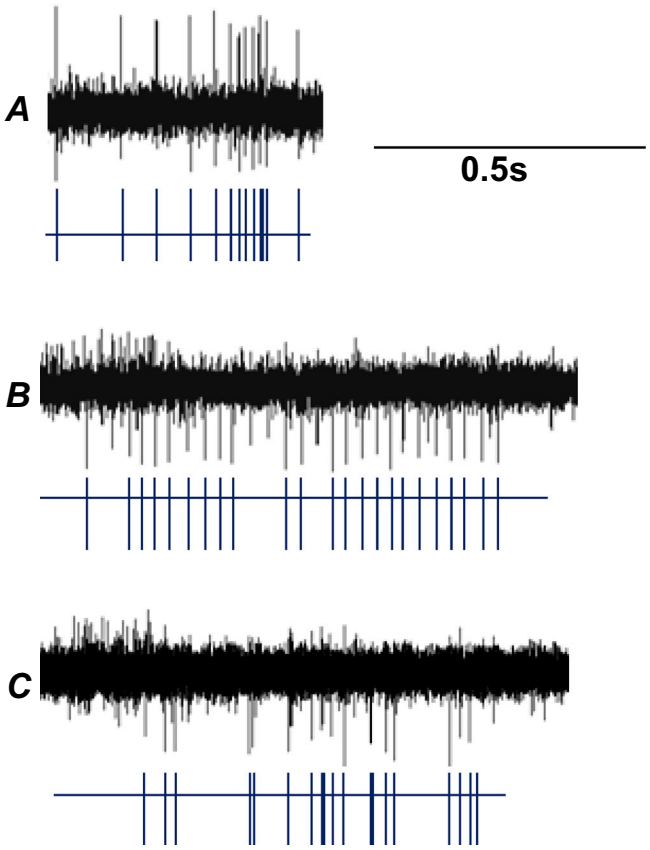

Figure 7. Examplar microneurography recording of afferent responses to the scratching stimuli in control participants
Single afferent recordings made using an insulated, tungsten microelectrode inserted into the peripheral nerve of a conscious human participant, as described in Nagi et al. 2019. Each afferent represented as a raw trace (above) and spike markers (below). Response to movement of the rough stimulus across the receptive field. *A*, low threshold, myelinated Aβ (field) afferent. *B*, C-nociceptor (high threshold, unmyelinated mechanoreceptor). *C*, C-tactile (low threshold, unmyelinated) mechanoreceptor.

First, the nature of the scratching stimulus (which, outside the context of itch, could be described as painful/noxious) suggests that preferential activation of high threshold mechanosensitive Aδ and/or C-fibre afferents contributes to the pleasure of scratching an itch in IW and, by inference, neurologically intact individuals. This is consistent with the wealth of scientific literature that documents either the prevention or abolishment/relief of itch by noxious cutaneous stimuli (Davidson et al., 2009; Schmelz, 2010; Bin Saif, Papoiu et al., 2012).

Second, slow gentle stroking stimuli that preferentially activate CT afferents are often associated with exacerbation or even recurrence of itch, that is, alloknesis (Fukuoka et al., 2013; LaMotte et al., 2009; Simone et al., 1991). In the present study, the pleasantness ratings of gentle stroking touch were significantly reduced when applied to itchy skin in neurologically intact participants, which lends support to our hypothesis that CT-mediated touch processing is altered in the context of itch; for example, as a result of CT afferents innervating itchy skin site undergoing a phenotypic switch in function. This is phenotypically comparable to dynamic mechanical allodynia (DMA) where gentle stroking touch applied to an area affected by pain is felt as unpleasant or outright painful (Bowsher 2005). However, the role of CT afferents in human DMA is uncertain. Evidence from most human studies suggests that an intact Aβ afferent system is necessary for the development of DMA (Baron & Maier, 1995; Koltzenburg et al., 1992; Liljencrantz et al., 2013; Nagi et al., 2011; Torebjörk et al., 1992). Individuals lacking Aβ fibres, including IW, do not develop overt allodynic features in the heat/capsaicin model of DMA (Liljencrantz et al., 2013). In the present study, IW did not experience alloknesis following itch induced by either cowage or histamine. This suggests that alloknesis is dependent on Aβ fibre input. Aβ fibre activity, probably via dorsal horn interneurons (Bourane et al., 2015; Ross, 2011; Westlund, 2006), rather than CT afferents, may contribute to the observed negative evaluation of gentle touch to itchy skin. However, this relationship is not unidirectional; for example, Ali et al. (2025) showed (in neurologically intact individuals) that CT–optimal stroking applied *adjacen*t to itchy skin reduced histamine–evoked itch sensation. This indicates that CT afferent input can influence pruriceptive signalling or pruriceptive perception, highlighting the contextual flexibility of tactile modulation of itch transmission or perception.

Finally, it could be argued that, in the absence of Aβ fibre input putatively inducing alloknesis, gentle stroking stimulation of itchy skin in IW, which would

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disproportionally activate CT afferents, should give rise to a hyperhedonic response. This was not the case. Thus, our findings suggest that activation of small-fibre, high-threshold mechanosensitive nociceptors – typically associated with a negative hedonic valance – contributes substantially to the pleasure associated with scratching an itch. In primates, the firing of histamine-responsive wide dynamic range (WDR) spinothalamic tract projection neurons following cutaneous application of this pruritogen (Davidson et al., 2009) is reduced by scratching for up to 30 s. This raises the possibility, at least in the context of acute itch, that both the relief and the pleasure of scratching is primarily modulated by the suppression of activity in ascending pruriceptive pathways (i.e. a relative change from a negatively-valued sensation to one that may be viewed as neutral). Interestingly, the effects of scratching on spinothalamic tract projection neurons were context specific. The very same histamine responsive cells showed an increased firing rate to rough mechanical stimulation after cutaneous capsaicin application. This suggests that the phenotypic output of ascending projections to the same stimulus can be modified depending on the pattern of inputs to the dorsal horn. Moreover, some WDR neurons have been shown to respond to both nociceptive and affective touch stimuli, including slow brushing (Andrew & Craig, 2001), raising the possibility that these neurons may serve as integrative hubs for both pruritic and hedonic signals. Such central convergence and integration could underlie the context-dependent modulation of scratching-induced pleasure observed in both control participants and in IW.

Although it is hypothesised that nociceptor activation is the primary peripheral modulator for the relief when scratching an itch, this does not exclude the possibility that the pleasurability of scratching, and the urge to scratch, are also mediated by coactivation of other mechanosensitive C- and Aδ fibres. There is increasing evidence of significant interactions between low-threshold mechanosensitive afferent inputs, and those signalling itch and nociceptive stimuli within the dorsal horn of the spinal cord. In rodents, itch suppression is mediated by several classes of inhibitory interneurons, including somatostatin-positive B5 cells responsive to mechanical and chemosensitive nociceptor input (Kardon et al., 2014; Ross et al., 2010), and neuropeptide-Y-positive inhibitory interneurons that integrate low-threshold mechanoreceptors (LTMRs) as well as pruriceptive signals (Bourane et al., 2015; Boyle et al., 2023; Pan et al., 2019). This suppression is consistent with the dorsal horn circuit organisation described by Abraira & Ginty (2013), where inhibitory interneurons within this region receive convergent input from Aβ, Aδ and C-LTMRs. Importantly, analogous circuit changes are well recognised in pain states, where alterations in inhibitory tone and excitatory drive within the dorsal horn contribute to central sensitisation and pathological pain, including hyperalgesia and mechanical allodynia (Smith & Ross, 2020; Zeilhofer & Ganley, 2019). Taken together, these findings suggest a mechanistic link: inhibitory interneuron networks in the LTMR zone normally act to dampen ascending itch signals, whereas changes in dorsal horn microcircuits, whether through disinhibition or altered projection neuron responsiveness, may shift the balance of tactile input toward a more complex hedonic experience, or conversely toward aversive sensations in pain states.

It is currently unclear whether a specific ascending projection pathway, potentially signalling hedonic aspects of touch and modifiable by nociceptive and pruriceptive stimuli, exists for C- or Aδ low-threshold tactile inputs. Studies in rodents have identified wide dynamic range spino-parabrachial tract projection neurons in lamina I of the dorsal horn that are responsive to slow caressing stimuli of the type that evoke vigorous firing in C-low threshold mechanoreceptor (C-LTMR) fibres, the equivalent of CT afferents in humans. These projection neurons, however, also respond to nociceptive stimuli (Andrew, 2010). Evidence of altered C-tactile processing induced by the heat-capsaicin model of dynamic mechanical allodynia has been provided in individuals lacking Aβ fibres (Liljencrantz et al., 2013). Although no overt allodynia was demonstrated, gentle stroking touch applied to the presumed allodynic zone was perceived as weaker than in control areas, but localisation was improved (as in our study on itch and rough stimulation). This was associated with altered activation of medial prefrontal cortex and posterior insula, regions important for CT afferent processing. It was argued that CT input was preferentially diverted to wide dynamic range pathways rather than putative labelled-line pleasant touch pathways. Theoretically, a related process could occur in the setting of pruritus, whereby itch and scratching might bias CT input away from wide dynamic range spinothalamic neurons and toward circuits more closely associated with hedonic touch processing. Human lesion studies provide further insight: Marshall et al. (2019) demonstrated that spinothalamic tract ablation abolished pain, temperature and itch but spared pleasant touch perception, indicating that hedonic aspects of touch are not conveyed by a privileged CT-spinothalamic pathway. Recent perspectives emphasise that CT afferents function as an emotional processing system rather than a simple labelled line (Schirmer et al., 2023). Human studies further show that hedonic responses to CT–mediated touch are strongly modulated by social and contextual factors (Novembre et al., 2021). Taken together, these findings suggest that itch states alter the integration of CT and other small-fibre mechanosensory inputs within ascending pruriceptive and affective pathways,

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contributing substantially to the context-dependent rewarding experience of scratching.

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Additional information

Data availability statement

All data supporting the results is presented in the final article.

Competing interests

The authors declare that they have no competing interests.

Author contributions

A.D.M., A.G.M., J.C. and F.P.M. were responsible for conceptualisation. A.D.M., A.G.M. and F.P.M. were responsible for methodology and investigations. A.D.M. was responsible for analysis. A.D.M. and F.P.M. were responsible for writing the original draft. A.D.M., A.G.M., J.C. and F.P.M. were responsible for reviewing and editing. A.D.M. was responsible for visualisation. F.P.M. was responsible for supervision and funding acquisition. All authors approved the final version of the manuscript submiited for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Generative AI statement

Microsoft M365 Copilot (GPT-5 chat model, June 2026) was used during manuscript revision to help assess the clarity, organisation and readability of text and figures produced by the authors. No generative AI tools were used for study design, data collection, data analysis, statistical calculations, figure generation, interpretation of results or generation of scientific conclusions. The authors take full responsibility for the accuracy and integrity of the work.

Keywords

affective touch, afferent nerve fibre, cutaneous afferent, itch, mechanoreceptors, pleasantness, somatosensory systems

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Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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